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(54) Title: PARTIAL LIQUID BREATHING OF FLUOROCARBONS

(57) Abstract

The present invention includes a method for treating a patient in need of facilitated oxygen delivery through the lungs, additional lung surfactant, removal of material from inside the lung, or inflation of collapsed portions of the lung, comprising the step of introducing into the lung of the patient an effective therapeutic amount of a fluorocarbon liquid, the amount not exceeding the functional residual capacity of the lung of the patient upon exhalation taking into account any positive and expiratory pressure applied to the patient's lung. The method may also comprise the additional step of providing an oxygen-containing breathing gas to the patient while the fluorocarbon liquid is in the lung.

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PARTIAL LIQUID BREATHING OF FLUOROCARBONS

FIELD OF THE INVENTION

5       The present invention relates generally to lung surfactant supplements and methods for treating pulmonary diseases. The invention specifically discloses partial liquid breathing techniques and the use of biocompatible liquid fluorocarbons in treatment of various pulmonary conditions.

BACKGROUND OF THE INVENTION

10      Lung surfactant is composed of a complex mixture of phospholipid, neutral lipid and protein. Surfactant is roughly 90% lipid and 10% protein with a lipid composition of 55% dipalmitoyl diphosphatidylcholine (DPPC), 25% phosphatidylcholine (PC), 12% phosphatidylglycerol (PG), 3.5% 15     Phosphatidylethanolamine (PE), sphingomyelin and phosphatidylinositol (PI).

20      Lung surfactant functions to reduce surface tension within the alveoli. It mediates transfer of oxygen and carbon dioxide, promotes alveolar expansion and covers the lung surfaces. Reduced surface tension permits the alveoli to be held open under less pressure. In addition, lung surfactant maintains alveolar expansion by varying surface tension with alveolar size (The Pathologic Basis of Disease, Robbins and Cotran eds. W.B. Saunders Co. New York, 1979). There are a number of medical therapies or regimes that would benefit from the use of surfactant supplements. For example, surfactant supplementation is beneficial for individuals with lung surfactant deficiencies. In addition, there are a variety of medical procedures requiring that fluids be added to the lung, 25     for example, as a wash to remove endogenous or exogenous matter. The use of a biocompatible liquid for these applications would be advantageous. Routinely, balanced salt solutions or balanced salt solutions in combination with a given therapeutic agent are provided as an aspirate or as a lavage for patients with asthma, cystic fibrosis or bronchiectasis. While balanced saline is biocompatible, lavage procedures can remove endogenous lung surfactant. Further,

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5 lavage with such aqueous liquids may not permit adequate delivery of oxygen to the body. Therefore, it is contemplated that the use of substances having at least some of the functional properties of lung surfactant could decrease lung trauma and provide an improved wash fluid.

10 At present, surfactant supplements are used therapeutically when the amount of lung surfactant present is not sufficient to permit proper respiratory function. Surfactant supplementation is most commonly used in  
15 Respiratory Distress Syndrome (RDS), also known as hyaline membrane disease, when surfactant deficiencies compromise pulmonary function. While RDS is primarily a disease of newborn infants, an adult form of the disease, Adult Respiratory Distress Syndrome (ARDS), has many of the same characteristics as RDS, thus lending itself to similar therapies.

20 Adult respiratory distress occurs as a complication of shock-inducing trauma, infection, burn or direct lung damage. The pathology is observed histologically as diffuse damage to the alveolar wall, with hyaline membrane formation and capillary damage. Hyaline membrane formation, whether in ARDS or RDS, creates a barrier to gas exchange. Decreased oxygen produces a loss of lung epithelium yielding decreased surfactant production and foci of collapsed alveoli. This  
25 initiates a vicious cycle of hypoxia and lung damage.

30 RDS accounts for up to 5,000 infant deaths per year and affects up to 40,000 infants each year in the United States alone. While RDS can have a number of origins, the primary etiology is attributed to insufficient amounts of pulmonary surfactant. Those at greatest risk are infants born before the 36th week of gestation having premature lung development. Neonates born at less than 28 weeks of gestation have a 60-80% chance of developing RDS. The maturity of the fetal lung is assessed by the lecithin/sphingomyelin (L/S) ratio in the amniotic fluid. Clinical experience indicates that when the  
35 ratio approximates 2:1, the threat of RDS is small. In those neonates born from mothers with low L/S ratios, RDS becomes a

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life-threatening condition.

At birth, high inspiratory pressures are required to expand the lungs. With normal amounts of lung surfactant, the lungs retain up to 40% of the residual air volume after the first breath. With subsequent breaths, lower inspiratory pressures adequately aerate the lungs since the lungs now remain partially inflated. With low levels of surfactant, whether in infant or adult, the lungs are virtually devoid of air after each breath. The lungs collapse with each breath and the neonate must continue to work as hard for each successive breath as it did for its first. Thus, exogenous therapy is required to facilitate breathing and minimize lung damage.

Type II granular pneumocytes synthesize surfactant using one of two pathways dependent on the gestational age of the fetus. The pathway used until about the 35th week of pregnancy produces a surfactant that is more susceptible to hypoxia and acidosis than the mature pathway. A premature infant lacks sufficient mature surfactant necessary to breathe independently. Since the lungs mature rapidly at birth, therapy is often only required for three or four days. After this critical period the lung has matured sufficiently to give the neonate an excellent chance of recovery.

In adults, lung trauma can compromise surfactant production and interfere with oxygen exchange. Hemorrhage, infection, immune hypersensitivity reactions or the inhalation of irritants can injure the lung epithelium and endothelium. The loss of surfactant leads to foci of atelectasis. Tumors, mucous plugs or aneurysms can all induce atelectasis, and these patients could therefore all benefit from surfactant therapy.

In advanced cases of respiratory distress, whether in neonates or adults, the lungs are solid and airless. The alveoli are small and crumpled, but the proximal alveolar ducts and bronchi are overdistended. Hyaline membrane lines the alveolar ducts and scattered proximal alveoli. The membrane consists of protein-rich, fibrin-rich edema admixed

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with cellular debris.

5       The critical threat to life in respiratory distress is inadequate pulmonary exchange of oxygen and carbon dioxide resulting in metabolic acidosis. In infants this, together with the increased effort required to bring air into the lungs, produces a lethal combination resulting in overall mortality rates of 20-30%.

10      Optimally, surfactant supplements should be biologically compatible with the human lung. They should decrease the surface tension sufficiently within the alveoli, cover the lung surface easily and promote oxygen and carbon dioxide exchange.

15      Ventilation assistance is commonly used to provide sufficient oxygen to surfactant deficient patients. These ventilation regimes include continuous positive airway pressure, or continuous distending pressure procedures.

20      Recently, surfactant replacement therapy has been used either alone or in combination with ventilation therapy. Initial work with surfactant replacements used preparations of human lung surfactant obtained from lung lavage. The lavaged fluid is collected and the surfactant layer naturally separates from the saline wash. This layer is harvested and purified by gradient centrifugation. These preparations worked well as surfactant replacements for RDS and thus provided some of the original data to suggest that surfactant replacement was a necessary therapy. Supplies of human surfactant are limited and expensive, and therefore alternate sources of surfactant were investigated for use in replacement therapies.

30      The second generation of surfactant substitutes are purified preparations of bovine and porcine lung surfactant. Preparations of bovine lung surfactant have been administered to many surfactant deficient patients. Like human surfactant, bovine lung surfactant is difficult to prepare. Sources are few and availability is limited. Further, while the use of bovine lung surfactant in neonates does not present a problem immunologically, bovine surfactant applications in adults

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could immunologically sensitize patients to other bovine products.

5 To minimize the immunologic problems associated with the use of bovine lung surfactant, the harvested surfactant is further extracted with chloroform/methanol to purify the lipid component. This work led to the discovery that there are three major proteins (SP-A, SP-B and SP-C) associated with lung surfactant. All three are postulated to have some beneficial role in surfactant function. SP-A is hydrophobic  
10 and has some documented antibacterial activity. SP-B is most closely associated with traditional surfactant function. These proteins can be purified or cloned, expressed and added back to purified lipid preparations. However, these procedures are also time consuming. In addition, the use of  
15 purified animal-derived surfactant protein creates the same immunologic problems noted above.

Some of the functional domains within each of the surfactant proteins are now mapped and the individual lipid components of lung surfactant are being tested to determine if 20 a semi-synthetic or synthetic product can be used effectively to replace purified endogenous surfactant. To this end, synthetic peptides of SP-B have been added to mixtures of DPPC and PG to create an artificial surfactant product.

An artificial surfactant would readily cover the lung 25 surfaces and facilitate oxygen exchange. The surfactant would be sterilizable, amenable to large scale production and be relatively stable for convenient storage and physician convenience.

Fluorocarbons are fluorine substituted hydrocarbons that 30 have been used in medical applications as imaging agents and as blood substitutes. U.S. Patent No. 3,975,512 to Long uses fluorocarbons, including brominated perfluorocarbons, as a contrast enhancement medium in radiological imaging. Brominated fluorocarbons and other fluorocarbons are known to 35 be safe, biocompatible substances when appropriately used in medical applications.

It is additionally known that oxygen, and gases in

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general, are highly soluble in some fluorocarbons. This characteristic has permitted investigators to develop emulsified fluorocarbons as blood substitutes. For a general discussion of the objectives of fluorocarbons as blood substitutes and a review of the efforts and problems in achieving these objectives see "Reassessment of Criteria for the Selection of Perfluorochemicals for Second-Generation Blood Substitutes: Analysis of Structure/Property Relationship" by Jean G. Reiss, Artificial Organs 8:34-56, 1984.

Injectable fluorocarbon emulsions act as a solvent for oxygen. They dissolve oxygen at higher tensions and release this oxygen as the partial pressure decreases. Carbon dioxide is handled in a similar manner. Oxygenation of the fluorocarbon when used intravascularly occurs naturally through the lungs. For other applications, such as percutaneous transluminal coronary angioplasty, stroke therapy and organ preservation, the fluorocarbon can be oxygenated prior to use.

Liquid breathing has been demonstrated on several occasions. An animal may be submerged in an oxygenated fluorocarbon liquid and the lungs may be filled with fluorocarbon. Although the work of breathing is increased in these total submersion experiments, the animal can derive adequate oxygen for survival from breathing the fluorocarbon liquid.

Liquid breathing as a therapy presents significant problems. Liquid breathing in a hospital setting requires dedicated ventilation equipment capable of handling liquids. Moreover, oxygenation of the fluorocarbon being breathed must be accomplished separately. The capital costs associated with liquid breathing are considerable.

It is an object of the present invention to provide a method for treating lung surfactant deficiency through use of fluorocarbon liquids.

A further object of the invention is to provide a method for therapeutic use of fluorocarbon liquids in the lungs that

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does not require liquid-handling ventilation equipment. Instead, traditional gas ventilation equipment can be used.

Still a further object of the present invention is to apply pulmonary administration of fluorocarbon liquids to a wide range of diseases and medical conditions.

These and other objects of the invention are discussed in the detailed description of the invention that follows.

SUMMARY OF THE INVENTION:

The present invention includes a method for treating a patient in need of facilitated oxygen delivery through the lungs, additional lung surfactant, removal of material from inside the lung, or inflation of collapsed portions of the lung, comprising the step of introducing into the lung of the patient an effective therapeutic amount of a fluorocarbon liquid, the amount not exceeding the functional residual capacity of the lung of the patient upon exhalation taking into account any positive and expiratory pressure applied to the patient's lung. The method may also comprise the additional step of providing an oxygen-containing breathing gas to the patient while the fluorocarbon liquid is in the lung.

In addition, a patient in need of additional lung surfactant may receive the fluorocarbon liquid as a lung surfactant replacement. In a preferred embodiment the amount of fluorocarbon liquid introduced into the lungs is at least about 0.1% of the patient's total lung capacity and not more than about 50% of the patient's total lung capacity, wherein the total lung capacity comprises the fluid volume of the lung when fully inflated during maximal inspiration. A preferred fluorocarbon is a brominated fluorocarbon and a still more fluorocarbon is perfluoroctylbromide. It is additionally contemplated that the equilibrium coefficient of spreading of the fluorocarbon is a positive number and more preferably that the equilibrium coefficient of spreading of the fluorocarbon be at least 1.0.

The amount of fluorocarbon liquid introduced into the patient's lung is contemplated to be at least 0.1 ml/kg of the

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patient's body weight and not more than about 50 ml/kg patient body weight.

It is further contemplated that the respiration of the patient while the fluorocarbon is in the lung can be facilitated by external ventilation equipment. In addition, it is contemplated that fluorocarbons can be used for partial liquid ventilation in patients having a respiratory distress syndrome and further that the method is effective to alleviate the respiratory distress syndrome. Another preferred use of fluorocarbon in the lung comprises the use of fluorocarbons for patients in need of removal of material from inside the lung, comprising the step of removing the fluorocarbon liquid, together with the material, from the lung. An additional method for the removal of material from the lung, comprises the steps of permitting the material to float on the fluorocarbon, and removing the floating material from the lung.

Fluorocarbon liquid can additionally be administered in combination with a pharmacologic agent in particulate form. It is further contemplated that the pharmacologic agent is a lung surfactant in powdered form. In addition, fluorocarbon is provided to patients in need of facilitated oxygen delivery through the lungs and for those patients receiving oxygen-containing breathing gas, it is contemplated that the oxygen containing breathing gas is oxygen.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1 is a graphic representation of the effect of intratracheal perfluoroctylbromide instillation of the blood oxygen levels in rabbits following lung lavage to remove endogenous surfactant as compared with intratracheal saline instillation.

Figure 2 is a graphic representation of the effect of intratracheal perfluoroctylbromide instillation on blood carbon dioxide levels in rabbits following lung lavage to remove endogenous surfactant.

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Figure 3 is a graphic representation of the effect of intratracheal perfluorooctylbromide instillation on mean and peak lung airway pressures in rabbits following lung lavage to remove endogenous surfactant.

5      DETAILED DESCRIPTION OF THE INVENTION

As noted, lung surfactant supplements should be non-toxic and biologically compatible. Like human surfactant, surfactant supplements should decrease the surface tension within the alveoli and promote oxygen and carbon dioxide exchange. Additionally these substitutes should spread easily over the lung surfaces to maximize gas interchange. Such a surfactant would enhance gas exchange, thus reducing cyanosis and metabolic acidosis.

Surfactant replacements that do not spread easily within the lung will tend to concentrate in pools and be less than optimally effective. Surfactant supplements should be readily available to the physician. In addition, they should be provided as a sterile product having reasonable chemical stability and a sufficient shelf-life.

20      Compounds useful in this invention, such as those listed below (hereinafter called "fluorocarbons") are generally able to promote gas exchange, and most of these fluorocarbons readily dissolve oxygen and carbon dioxide. There are a number of fluorocarbons that are contemplated for medical use.

25      These fluorocarbons include bis(F-alkyl) ethanes such as  $C_4F_9CH=CH_2CF_3$ , (sometimes designated "F-44E"), i- $C_3F_9CH=CHC_6F_{13}$  ("F-i36E"), and  $C_6F_{13}CH=CHC_6F_{13}$  ("F-66E"); cyclic fluorocarbons, such as ClO<sub>2</sub>F<sub>18</sub> ("F-decalin", "perfluorodecalin" or "FDC"), F-adamantane ("FA"), F-methyladamantane ("FMA"), F-1,3-dimethyladamantane ("FDMA"), F-di- or F-trimethylbicyclo[3.3.1]nonane ("nonane"); perfluorinated amines, such as F-tripropylamine ("FTPA") and F-tri-butylamine ("FTBA"), F-4-methyloctahydroquinolizine ("FMOQ"), F-n-methyl-decahydroisoquinoline ("FMIQ"), F-n-methyldecahydroquinoline ("FHQ"), F-n-cyclohexylpurrolidine ("FCHP") and F-2-butyltetrahydrofuran ("FC-75" or "RM101").

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Other fluorocarbons include brominated perfluorocarbons, such as 1-bromo-heptadecafluoro-octane ( $C_8F_{17}Br$ , sometimes designated perfluoroctylbromide or "PFOB"), 1-bromopenta-decafluoroheptane ( $C_7F_{15}Br$ ), and 1-bromotridecafluorohexane ( $C_6F_{13}Br$ , sometimes known as perfluorohexylbromide or "PFHB").  
5 Other brominated fluorocarbons are disclosed in US Patent No. 3,975,512 to Long. Also contemplated are fluorocarbons having nonfluorine substituents, such as perfluoroctyl chloride, perfluoroctyl hydride, and similar compounds having different numbers of carbon atoms. In addition, the fluorocarbon may be  
10 neat or may be combined with other materials, such as surfactants (including fluorinated surfactants) and dispersed materials.

Additional fluorocarbons contemplated in accordance with this invention include perfluoroalkylated ethers or polyethers, such as  $(CF_3)_2CFO(CF_2CF_2)_2OCF(CF_3)_2$ ,  $(CF_3)_2CFO-(CF_2CF_2)_3OCF(CF_3)$ ,  $(CF_3)CFO(CF_2CF_2)F$ ,  $(CF_3)_2CFO(CF_2CF_2)_2F$ ,  $(C_6F_{13})_2O$ . Further, fluorocarbon-hydrocarbon compounds, such as, for example compounds having the general formula  $C_nF_{2n+1}-C_{n'}F_{2n'+1}$ ,  $C_nF_{2n+1}OC_{n'}F_{2n'+1}$ , or  $C_nF_{2n+1}CF=CHC_{n'}F_{2n'+1}$ , where n and n' are the same or different and are from about 1 to about 10 (so long as the compound is a liquid at room temperature). Such compounds, for example, include  $C_8F_{17}C_2H_5$  and  $C_6F_{13} CH=CHC_6H_{13}$ . It will be appreciated that esters, thioethers, and other variously modified mixed fluorocarbon-hydrocarbon compounds are also encompassed within the broad definition of "fluorocarbon" materials suitable for use in the present invention. Mixtures of fluorocarbons are also contemplated.  
25 Additional "fluorocarbons" not listed here, but having those properties described in this disclosure that would lend themselves to pulmonary therapies are additionally contemplated.  
30

Some fluorocarbons have relatively high vapor pressures which render them less suitable for use as a surfactant replacement and for partial liquid breathing. These include 1-bromotridecafluorohexane ( $C_6F_{13}Br$ ) and F-2-butyltetrahyddrofuran ("FC-75" or "RM101"). Lower vapor

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pressures are additionally important from an economic standpoint since significant percentages of fluorocarbon having high vapor pressure would be lost due to vaporization during the therapies described herein. In a preferred embodiment, fluorocarbons having lower surface tension values are chosen as surfactant supplements.

The fluorocarbon of choice should have functional characteristics that would permit its use temporarily as a lung surfactant, for oxygen delivery, in removal of material from the interior of the lung, or for inflation of collapsed portions of the lung. Fluorocarbons are biocompatible and most are amenable to sterilization techniques. For example, they can be heat-sterilized (such as by autoclaving) or sterilized by radiation. In addition, sterilization by ultrafiltration is also contemplated.

One group of preferred fluorocarbons have the ability to reduce the surface tension in the lung. As noted above, surfactants function to decrease the tension between the surface molecules of the alveolar fluid. The lung surfactant is solubilized in a water-continuous fluid lining the alveolus. Typically, the surface tension in the absence of lung surfactant is ca. 60 dynes/cm decreasing to 5-30 dynes/cm in the presence of lung surfactant. Fluorocarbons have low surface tension values (typically in the range of 20 dynes/cm) and have the added benefit of dissolving extremely large quantities of gases such as oxygen and carbon dioxide. Perfluorocarbons are particularly suited for this use, and brominated fluorocarbons are particularly preferred.

Although reduction in surface tension is an important parameter in judging fluorocarbons and perfluorocarbons as potential lung surfactant supplements or for use in partial liquid breathing, a novel and non-obvious characteristic of some fluorocarbons is their apparent ability to spread over the entire respiratory membrane. The ability of some fluorocarbons to spread evenly and effectively over lung surfaces may be of even greater importance than the ability of fluorocarbons to reduce surface tension.

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The total surface area of the respiratory membrane is extremely large (ca. 160 square meters for an adult). Thus, an effective fluorocarbon for partial liquid breathing should be able to cover the lung surfaces with relatively little  
5 volume.

The ability of a given substance to cover a measured surface area can be described by its spreading coefficient. The spreading coefficients for fluorocarbons can be expressed by the following equation:

10  $S \text{ (o on w)} = \gamma_{w/a} - (\gamma_{w/o} + \gamma_{o/a})$

Where  $S \text{ (o on w)}$  represents the spreading coefficient;  $\gamma$  = interfacial tension;  $w/a$  = water/air;  $w/o$  = water/oil; and  $o/a$  = oil/air.

If the fluorocarbon exhibits a positive spreading coefficient, then it will spread over the entire surface of the respiratory membrane. Fluorocarbons having spreading coefficients of at least one are particularly preferred. If the spreading coefficient is negative, the compound will tend to remain as a lens on the membrane surface. Adequate coverage  
15 of the lung surface is important for restoring oxygen and carbon dioxide transfer and for lubricating the lung surfaces to minimize further pulmonary trauma.  
20

The spreading coefficients for a number of perfluorocarbons are reported in Table 1. Each perfluorocarbon tested is provided together with its molecular weight and the specific variables that are used to calculate the spreading coefficient  $S \text{ (o on w)}$ . The perfluorocarbons reported are PFOB, perfluorotributylamine (FC-17), perfluorodecalin (APF-140), dimethyl perfluorodecalin (APF-  
25 175), trimethyl decalin (APF-200), perfluoroperhydrophenanthrene (APF-215), pentamethyl decalin (APF-240), and octamethyl decalin (APF-260).

These perfluorocarbons are representative of groups of perfluorocarbons having the same molecular weight that would produce similar spreading coefficients under similar experimental conditions. For example, it is expected that ethyl perfluorodecalin will have a spreading coefficient  
30

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similar to that of dimethylperfluorodecalin. Propyl or other  
3 carbon-substituted decalin would have a spreading  
coefficient similar to that reported for trimethyl decalin,  
pentamethyldecalin is representative of other decalins  
5 substituted with 5 substituent carbons, and octamethyldecalin  
is also representative of other combination substituted  
decalins of identical molecular weight.

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TABLE I  
Spreading coefficients of perfluorocarbons on saline (T=25 C)

Perfluorocarbon	MW (g/mol)	$\gamma_{o/w}$ (mN/m)	$\gamma_{o/w}$ (mN/m)	S ( $\sigma$ on w)
PFOB	499	18.0	51.3	+2.7
(perfluoroctylbromide)				
FC-47	671	17.9	55.1	-1.0
(perfluorotributylamine)				
APF-140	468	18.2	55.3	-1.5
(perfluorodecalin)				
APF-175	570	20.7	55.9	-4.6
(dimethyl decalin)				
APF-200	620	21.4	55.9	-5.3
(trimethyl decalin)				
APF-215	630	21.6	56.0	-5.6
(perfluoroperhydrophenanthrene)				
APF-240	770	22.6	56.3	-6.9
(pentamethyl decalin)				
APF-260	870	22.4	56.1	-6.5
(octamethyl decalin)				

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It can be seen from this limited sampling of fluorocarbons that perfluoroctylbromide (PFOB) provides a positive spreading coefficient. In addition, PFOB has a low vapor pressure (14 torr @ 37°C), further illustrating that PFOB is a particularly preferred choice for use as a lung surfactant replacement. Because of the reduced vapor pressure, PFOB will have a decreased tendency to vaporize during use. Perfluorodecalin (APF-140) and perfluoroamine (FC-47) have also been tested in potential blood substitute formulations. These compounds exhibit negative spreading coefficients on saline. However, other perfluorocarbons, similar to APF-140 and FC-47, but having decreasing molecular weights, exhibited decreasing surface tensions and increasing spreading coefficients. This suggests that lower molecular weight perfluorocarbons might also have useful spreading coefficients. However, decreasing molecular weight will increase vapor tension and make the compounds less suitable for this use.

The following examples provide information relating to the effect of PFOB treatment on respiratory insufficiency in an experimental rabbit model. The general protocol for partial liquid ventilation of the rabbits is described below.

Animal Preparation

New Zealand rabbits weighing between 2.8 and 3.0 kg were anesthetized with 50 mg/kg of phenobarbital sodium iv and a cannula was inserted through a tracheotomy midway along the trachea with its tip proximal to the carina. Ventilation with a Servo ventilator 900C (Siemens-Elema, Sweden) was initiated using pure oxygen and zero end-expiratory pressure with a constant tidal volume of 12 ml/kg, frequency of 30/min and inspiratory time of 35%. Anesthesia was maintained with additional doses of pentobarbital, as required, and pancuronium bromide was administered as an intravenous bolus (0.1mg/kg) and followed by a continuous infusion (0.1mg/kg/hr) for muscle paralyzation. A solution of 5% dextrose and 0.45% NaCl was administered continuously at a

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rate of 10ml/kg/hr as a maintenance fluid. A heating pad maintained core temperature at  $37\pm1^{\circ}\text{C}$ , monitored by an esophageal thermistor (Elektroalboratoriet, Copenhagen).

5 Left femoral artery and vein were each cannulated with polyvinyl catheters for arterial and central venous pressure recording and blood sampling. A special indwelling catheter (Mikro- $\text{PO}_2$ -Messkatheter, Licox) was inserted into the right femoral artery for continuous oxygen pressure monitoring (Licox, GMS, Germany). Arterial blood gas hemoglobin and 10 hemoglobin saturation (hemoglobin) measurements were made using OSM-2 Hemoximeter and ABL-330 (Radiometer Copenhagen). Lung mechanics and end-tidal  $\text{CO}_2$  were measured by means of Lung Mechanics Calculator 940 (Siemens-Elema, Sweden) and  $\text{CO}_2$  Analyzer 930 (Siemens-Elema, Sweden), respectively. 15 Intravascular pressure monitoring was performed using a Statham P23XL transducer (Spectramed, USA) and all tracings including ECG were recorded by a Sirecust 1280 recorder (Siemens).

Model of Respiratory Insufficiency

20 After the control observations were made, lung lavage with 30ml/kg of warm saline ( $37^{\circ}\text{C}$ ) was performed to induce respiratory insufficiency. After the first lavage, positive end expiratory pressure (PEEP) was increased to 6  $\text{cmH}_2\text{O}$  and lung lavages were repeated to get an arterial  $\text{pO}_2$  below 100 25 mmHg with the initial ventilatory settings (between 4-6 lavages). The same ventilation mode was used throughout the experiment (volume control ventilation;  $\text{F}_1\text{O}_2$ : 1, tidal volume: 12ml/kg, PEEP: 6  $\text{cm H}_2\text{O}$ , frequency: 30/min, inspiratory time: 35%).

30 Partial Liquid Ventilation Procedure:

After respiratory insufficiency was induced, PFOB liquid was administered through the tracheal cannula into the animal's lungs with incremental doses of 3 ml/kg up to a total volume of 15 ml/kg. Animals were ventilated for 15 35 minutes after each dose of PFOB instillation with the same ventilatory settings as mentioned above and thereafter arterial blood gases, cardiocirculatory parameters and

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pulmonary mechanics were measured. After the last dose PFOB measurements, animals were sacrificed by administration of high dose pentobarbital.

Example 1

5      Mean arterial oxygen tensions following PFOB administration

Figure 1 is a graphic representation of the results of the experimental protocol described above. The mean arterial oxygen tension in the six rabbits tested was 504.2 mmHg. Following lung lavage to remove surfactant the arterial oxygen tension dropped to a mean value of 75.1 mmHg. The administration of increasing volumes of PFOB resulted in increasing arterial oxygen tensions. Doses of 15ml/kg of PFOB increased oxygen pressures to 83% of their original value. These results are compared to the use of saline for partial liquid ventilation. Increasing volumes of saline in place of PFOB yielded an additional drop in arterial oxygen pressure. This data indicates that the administration of the perfluorocarbon PFOB significantly improved the arterial oxygen tension in the experimental animals as compared to saline treated controls.

Example 2

25      Mean arterial carbon dioxide tensions following PFOB administration

Mean arterial carbon dioxide tensions were calculated following lung lavage using the experimental protocol described above. Figure 2 is a graphic representation of these results. Before lavage the average arterial carbon dioxide tensions in the lungs was 37 mmHg. Following the lavage procedure the carbon dioxide levels increased to 48.7 mmHg. This level decreased after administration of PFOB, indicating that CO<sub>2</sub> elimination was also facilitated by PFOB administration.

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Example 3

Mean airway pressures following PFOB administration

Mean airway pressures were determined following PFOB supplementation of surfactant deficient animals. Figure 3 shows mean airway pressures measured in  $\text{cmH}_2\text{O}$  as a function of increasing volumes of PFOB added. Following lung lavage the airway pressures increased due to surfactant depletion. PFOB supplementation decreased mean airway pressure.

- 10 The data for Examples 1-3 are provided in Table 2.

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INTRATRACHEAL PFOB ml/kg						
		BEFORE LAVAGE	ARDS	3	6	9
$P_aO_2$ mmHg	X	504.2	75.1	159.6	296.7	365.7
	SD	39.7	15.0	38.1	54.4	33.4
$P_aCO_2$ mmHg	X	37.0	48.7	42.8	44.4	45.0
	SD	2.6	6.0	4.7	4.8	4.6
Peak Airway Pressure cmH <sub>2</sub> O	X	12.4	25.5	21.3	20.6	20.6
	SD	1.4	1.0	1.4	1.2	1.6

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Both fetal and adult rabbits have been used to study Respiratory Distress Syndrome. Much of the work with surfactant replacements was initiated in these animals. For studies on RDS therapies, the method of fetal animal ventilation used should closely mimic the ventilation methods used for the neonate. Other fetal and adult animals studied include lamb, dog or baboon. In vivo studies in animals are necessary to correlate the in vitro characteristics of a given fluorocarbon with its in vivo benefits.

An analysis of the therapeutic benefit or the usefulness of a given fluorocarbon or a lung additive containing fluorocarbon necessarily includes an analysis of a number of experimental parameters. These parameters include measurements of dynamic lung compliance, blood gas quantitations, alveolar/arterial oxygen tension ratios, lung water estimates, vascular protein leakage into the lung, inflammatory cell infiltrates, chest radiographs, ventilatory support indices over time and the like. Lung histologies from experimental subjects are used to demonstrate the resolution of atelectasis, evidence of necrosis, desquamation and inflammation. Individuals skilled in the art will be familiar with the test parameters listed above, therefore no further information needs be provided to facilitate these tests. Fluorocarbons providing beneficial test results in experimental animals are candidates for human use.

It is contemplated that there are a variety of uses for fluorocarbons in partial liquid breathing applications. Lung lavage can be used as both a diagnostic and therapeutic procedure. Diagnostic washings are often obtained by bronchoscopy. Diagnostic lavage requires the introduction of a small amount of fluid into the lungs in order to sample lung cells, exudate, or to obtain a sample for microbiological analysis.

Therefore, in accordance with one aspect of this invention, it is contemplated that PFOB or another

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fluorocarbon meeting the positive criteria disclosed herein could be used for such a procedure.

5 Large volume lung lavage is sometimes used as an emergency procedure to remove irritants, poisons or mucous plugs from the lungs. The procedure is also used in neonates to remove aspirated meconium. A pulmonary catheter is inserted into the bronchial airway and a solution is flushed into the lung. The use of saline in the lung for large volume lavage creates several problems. The procedure must be performed quickly because oxygen transfer at the membrane/air interface cannot occur efficiently in the presence of saline, and large volumes of saline flushed into the lungs effectively dilute and remove any functional lung surfactant present.

10 15 It is also contemplated that fluorocarbons could be used to inflate collapsed portions of lungs or collapsed lungs in general. The use of fluorocarbon to inflate portions of the lung is less damaging than the current methods employing increased air pressure. As noted previously, increased air pressures in lungs, particularly lungs that are compromised by disease or trauma, can produce barotrauma and induce additional lung damage.

20 25 If the lungs have been compromised by an irritant then surfactant replacement may be necessary. Oxygenatable fluorocarbons with positive spreading coefficients and low vapor pressures could provide an improved lavage fluid.

30 The fluorocarbon could also be provided as a liquid or aerosol in combination with an expectorant. The biocompatible fluorocarbon is easily taken into the lung and the expectorant additive facilitates the removal of the secretions of the bronchopulmonary mucous membrane. Examples of contemplated expectorants include but are not limited to ammonium carbonate, bromhexine hydrochloride and terpin hydrate.

35 In accordance with another aspect of this invention, it is further contemplated that PFOB or another suitable

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fluorocarbon could be used as a surfactant supplement. PFOB is able to spread easily over the surfaces of the lung and can facilitate oxygen transport. Any condition characterized by a lung surfactant deficiency would be amenable to this therapy. In addition to RDS in neonates, ARDS in adults caused by severe hypovolemic shock, lung contusion, diver's lung, post-traumatic respiratory distress, post-surgical atelectasis, septic shock, multiple organ failure, Mendelsohn's disease, obstructive lung disease, pneumonia, pulmonary edema or any other condition resulting in lung surfactant deficiency or respiratory distress are all candidates for fluorocarbon supplementation.

The amount of surfactant supplement given should be sufficient to cover the lung surface and should be at least 0.1% of the infant or adult's total lung capacity. In RDS, it is particularly important to stabilize the infant while minimizing and preventing additional lung damage for roughly four or five days. Those infants with RDS that survive this critical time frame have an 80% survival rate. The fluorocarbon is provided by direct instillation through an endotracheal tube. If the fluorocarbon is provided together with a surfactant liquid or powder, the powder can either be mixed into the fluorocarbon or provided to the infant or adult as an aerosol prior to fluorocarbon administration. The addition of lung surfactant to fluorocarbon provides a surfactant dispersed throughout the fluorocarbon liquid.

During administration if it is desired to only ventilate one lung with liquid, the intubated infant is placed in the right and left lateral decubitus positions while being mechanically or manually ventilated. Since neonates are often difficult to intubate, only those individuals experienced in neonatal intubation should attempt this procedure. Mechanical ventilator usage and initial settings of breaths/minute, positive inspiratory pressures, positive-end expiratory pressure and inspiratory durations should be set initially as determined by the known standards for given

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infant weight and gestational ages, but should be monitored closely and altered accordingly as pulmonary function improves.

5       The use of partial liquid breathing is not restricted to cases where lung surfactant supplementation is necessary. Any condition requiring facilitated oxygen delivery is amenable to the use of partial liquid breathing. Because the volume of fluorocarbon in the lung is such that liquid fluorocarbon is not exhaled by the patient, conventional ventilation equipment can be used. This overcomes a major 10 obstacle to liquid breathing as contemplated in the prior art.

15      In addition to oxygen delivery, fluorocarbons can be used to remove endogenous or foreign material from the interior of the lungs. Lavage can be practiced using fluorocarbons as a substitute for conventional saline solutions. In this procedure, oxygen is provided to the patient by the fluorocarbon liquid itself, permitting a more lengthy and less dangerous lavage procedure. Moreover, 20 removal of lung surfactant through the lavage is not a major problem because of the lung surfactant properties of selected fluorocarbons. The lavage procedure is further facilitated by the density of the fluorocarbon. The density of these liquids is generally near 2, that is, twice that of water; they therefore tend to displace the material to be removed. 25 This material can then be removed by removing the fluorocarbon, or can be removed from the surface of the fluorocarbon on which it will generally float.

30      In addition to the lung surfactant properties, the density of the fluorocarbon can facilitate inflation of collapsed alveoli and other portions of the lung. Under the influence of gravity, the fluorocarbon will apply positive pressure above and beyond breathing pressure to inflate such collapsed portions of the lung.

35      The use of fluorocarbons for partial liquid breathing requires a volume as little as 0.1% of the total lung

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capacity upon full natural inflation. However, it is preferred that the amount used be at least 0.2%, and more preferably at least 0.3% or 0.5% of the total lung capacity. Minimum amounts of 1%, 3%, or 5% of total lung capacity are 5 preferred. It is additionally contemplated that fluorocarbon could be added in amounts up to about 50% of the total lung capacity.

Thus a method for partial liquid breathing is provided as another aspect of this invention.

10 Partial liquid breathing has a number of benefits over the total liquid breathing methods contemplated primarily for use in neonates. It appears that the difficult transition from total liquid breathing to total air breathing can be reduced by partial liquid breathing. The lungs are bathed in 15 a biocompatible fluid. Lung trauma is minimized and this permits lung maturation and repair. Partial liquid breathing is more amenable to use than total liquid breathing since air or gas can still be inhaled and exhaled. Partial liquid breathing can be used in conjunction with spontaneous, 20 passive or mechanical ventilation. In addition, pharmacologic substances can be added to the fluorocarbon to further promote resolution of lung injury.

The amount of fluorocarbon introduced into the patient's lung is, at a minimum, necessarily sufficient to cover the 25 surfaces of the lung. The actual volumes will depend on the treatment protocol, the weight and size of a patient as well as the lung capacity. It is contemplated that the useful range of fluorocarbon should be at least 0.1 ml of fluorocarbon liquid per kilogram patient body weight and not 30 more than about 50 ml/kg.

It is further preferred that the maximum amount of fluorocarbon used for partial liquid breathing will approximate the volume of air remaining in a healthy lung of similar size following passive exhalation, taking into account any positive or negative end expiratory pressure 35 applied. Air or other respiration gases remaining in the lung

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at the end of exhalation can be measured in a number of ways that are known by those with skill in the art. Physiology-related equations relate the size, age, or weight of an individual to his exhaled lung volume.

5 Thus, during partial liquid breathing in accordance with the present invention, the lungs retain sufficient air capacity (above and beyond the volume of fluorocarbon in the lung) to permit inhalation such that normal breathing can proceed. Air or other respired gases entering the lungs on 10 inhalation is sufficient to oxygenate the fluorocarbon liquid. Further, the fluorocarbon liquid may be oxygenated prior to use to provide oxygen to the alveolar surfaces of the lung instantaneously upon initial contact with the fluorocarbon. If ventilation therapy is required, unlike 15 total liquid breathing, standard ventilation equipment can be used. Partial liquid breathing can be used to reverse ventilatory failure, as a prophylactic to prevent respiratory failure or as a therapeutic. As a therapeutic, fluorocarbon solution can be administered alone to minimize further lung trauma, or in combination with a given therapeutic agent. 20 Fluorocarbon liquid can be provided together with a particulate therapeutic agent such as lung surfactant. These powder surfactants may be synthetic mixtures of phospholipids. For example, a mixture of 25 diphosphatidylcholine and phosphoglycerol in a ratio of 7:3 could be mixed with a volume of fluorocarbon. Additionally, the surfactant powder may be in the form of dried extracts prepared from human or animal lung lavage. It was noted earlier that there are three major proteins (SP-A, SP-B and 30 SP-C) associated with endogenous lung surfactant. Therefore, it is additionally contemplated that these proteins may be added as full length or as truncated fragments to the fluorocarbon mixture.

35 Partial liquid breathing according to the present invention is useful for a variety of medical applications. As a lavage, the technique is useful for meconium aspiration,

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gastric acid aspiration, asthma, cystic fibrosis, and pneumonia to remove adventitious agents. A fluorocarbon lavage may also be provided to patients with pulmonary alveolar proteinosis, bronchiectasis, atelectasis and 5 immotile cilia syndrome. In addition, fluorocarbon may be used in emergency lavage procedures to remove food aspirates, gastric acid, and other foreign materials.

Loss of lung resiliency can occur in both ARDS and RDS. The use of fluorocarbons in both of these syndromes is 10 discussed above. In addition, lungs can become stiff from hydrocarbon aspiration, smoke inhalation, and lung contusions. Fluorocarbon therapy can be provided either as a surfactant supplement or for partial liquid breathing to supply oxygen to a patient or to facilitate a therapeutic 15 regime. Treatment of pulmonary fibrosis, emphysema, and chronic bronchitis can all benefit from fluorocarbon therapy.

It has been noted above that a fluorocarbon liquid may be supplied to a patient in combination with a powdered surfactant or as a route for pulmonary drug delivery. 20 Antibiotics and antivirals may be provided in combination with a fluorocarbon liquid. For example, cytomegalovirus can induce life-threatening cases of pneumonia in immunocompromised patients. These individuals often require ventilation therapy. Fluorocarbon administration in 25 combination with the guanosine nucleoside analog, 9-(1,3-dihydroxy-2-propoxymethyl)guanine otherwise known as Ganciclovir or DHPG, may provide an effective therapy that could simultaneously inhibit viral replication and facilitate oxygen transport in the compromised lung.

In addition, anti-inflammatory agents could be added alone or in combination to the antimicrobial agents contemplated above. These anti-inflammatory agents include but are not limited to steroid and steroid derivatives or analgesics. The fluorocarbon could be administered together 35 with a bronchodilator including but not limited to Albuterol, Isoetharines, perbuteral or an anti-allergenic agent.

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5       The various pharmaceuticals that can be combined with fluorocarbons to provide therapy via administration to the lungs are too numerous to list. Except in some particularly preferred embodiments listed herein, the choice of pharmaceutical is not critical. Any non-damaging pharmaceutical that can be adsorbed across the lung membranes, or that can treat lung tissue, can be used. The amounts and frequency of administration for all the various possible pharmaceuticals have been established. It is not contemplated that these will be significantly different for administration through use of fluorocarbon vehicles in partial liquid breathing. Thus, those of ordinary skill in the art can determine the proper amount of pharmaceutical and the timing of the dosages in accordance with already-existing 10 information and without undue experimentation.

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20       The fluorocarbon liquid may also be administered in combination with an antimitotic agent for cancer therapy. Fluorocarbon liquid can also be used to facilitate oxygenation under anesthesia for patient's suffering from lung diseases such as emphysema, chronic bronchitis, and pulmonary fibrosis or who have undergone resection of substantial amounts of lung tissue. Furthermore, fluorocarbons can be used for partial liquid breathing for any of the above mentioned maladies or any additional medical 25 condition that would lend itself to this therapy.

30       The fluorocarbon liquid may advantageously be supplied to the physician in a sterile prepackaged form. Aliquots of the fluorocarbon are removed for administration under sterile conditions. Individual dosage volumes can be supplied for administration to newborns since newborn lung capacities are within a fairly narrow range. For those applications requiring a mixture of fluorocarbon and saline or powdered surfactant, each component can be provided separately and prepared for individual use. For lavage purposes, neat fluorocarbon or prepared emulsions of fluorocarbon and saline 35 are provided prepackaged. It will be readily appreciated

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that there are a large number of potential additives that, in combination with fluorocarbon liquid, have important medical applications in the lung.

Those with skill in the art will readily appreciate the varied applications for fluorocarbon administration. Therefore the foregoing detailed description is to be clearly understood as given by way of illustration, the spirit and scope of this invention being limited solely by the appended claims.

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WHAT IS CLAIMED IS:

1. The use of a composition comprising a liquid fluorocarbon for the manufacture of a medicament for the treatment of respiratory diseases.
- 5 2. Use according to Claim 1 wherein said medicament is applied together with an oxygen-containing gas to facilitate oxygen delivery to the body through the lungs.
- 10 3. Use according to Claim 1 or 2 wherein said medicament is used as a pulmonary lavage to remove material from the pulmonary passages, to inflate collapsed portions of a lung, or to replace lung surfactant.
- 15 4. Use according to Claim 1 or 2, wherein said fluorocarbon is a brominated fluorocarbon.
5. Use according to Claim 1, 2, or 4, wherein said composition further comprises a pharmacological agent.
- 15 6. Use according to Claim 5, wherein said pharmacological agent is a hydrophilic lung surfactant.
- 20 7. Use according to Claim 1, 2, or 4, wherein said medicament is used in connection with a mechanical breathing apparatus.
- 25 8. A method of treating a patient in need of facilitated oxygen delivery through the lungs, additional lung surfactant, removal of material from inside the lung, or inflation of collapsed portions of the lung, comprising the step of introducing into the lung of the patient an effective therapeutic amount of a fluorocarbon liquid, said amount not exceeding the functional residual capacity of the lungs of the patient upon exhalation taking into account any positive or negative expiratory pressure applied to said patient's lung.
- 30 9. The method of Claim 8, further comprising the step of providing an oxygen-containing breathing gas to the patient while said fluorocarbon liquid is in the lung.

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10. The method of Claim 9, wherein the patient is in need of additional lung surfactant and the fluorocarbon liquid serves as lung surfactant replacement.

5 11. The method of Claim 9, wherein the amount of fluorocarbon liquid introduced is at least about 0.1% of the patient's total lung capacity and not more than about 50% of the patient's total lung capacity, wherein total lung capacity comprises the fluid volume of the lung when mechanically inflated.

10 12. The method of Claim 9, wherein the fluorocarbon is a brominated fluorocarbon.

13. The method of Claim 5, wherein the fluorocarbon is perfluoroctylbromide.

15 14. The method of Claim 3, wherein the equilibrium coefficient of spreading of said fluorocarbon is a positive number.

15 15. The method of Claim 7, wherein the equilibrium coefficient of spreading of said fluorocarbon is at least 1.0.

20 16. The method of Claim 9, wherein the amount of fluorocarbon liquid introduced into the patient's lung is at least 0.1 ml/kg of said patient's body weight and not more than about 50 ml/kg patient body weight.

25 17. The method of Claim 9, further comprising the step of facilitating respiration by said patient while said fluorocarbon is in the lung with external ventilation equipment.

30 18. The method of Claim 8, wherein said patient has a respiratory distress syndrome and said method is effective to alleviate said respiratory distress syndrome.

19. The method of Claim 8, wherein said patient is in need of removal of material from inside the lung, further comprising the step of removing said fluorocarbon liquid, together with said material, from the lung.

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20. The method of Claim 8, wherein said patient is in need of removal of material from the lung, further comprising the steps of:

5 permitting said material to float on said fluorocarbon;

and

removing said floating material from the lung.

10 21. The method of Claim 8, wherein said fluorocarbon liquid further comprises a pharmacologic agent in particulate form and delivers said agent to the lungs of said patient.

22. The method of Claim 21, wherein said pharmacologic agent is a hydrophilic lung surfactant in powdered form.

23. The method of Claim 9, wherein said patient is in need of facilitated oxygen delivery through the lungs.

15 24. The method of Claim 9, wherein said oxygen-containing breathing gas is oxygen.

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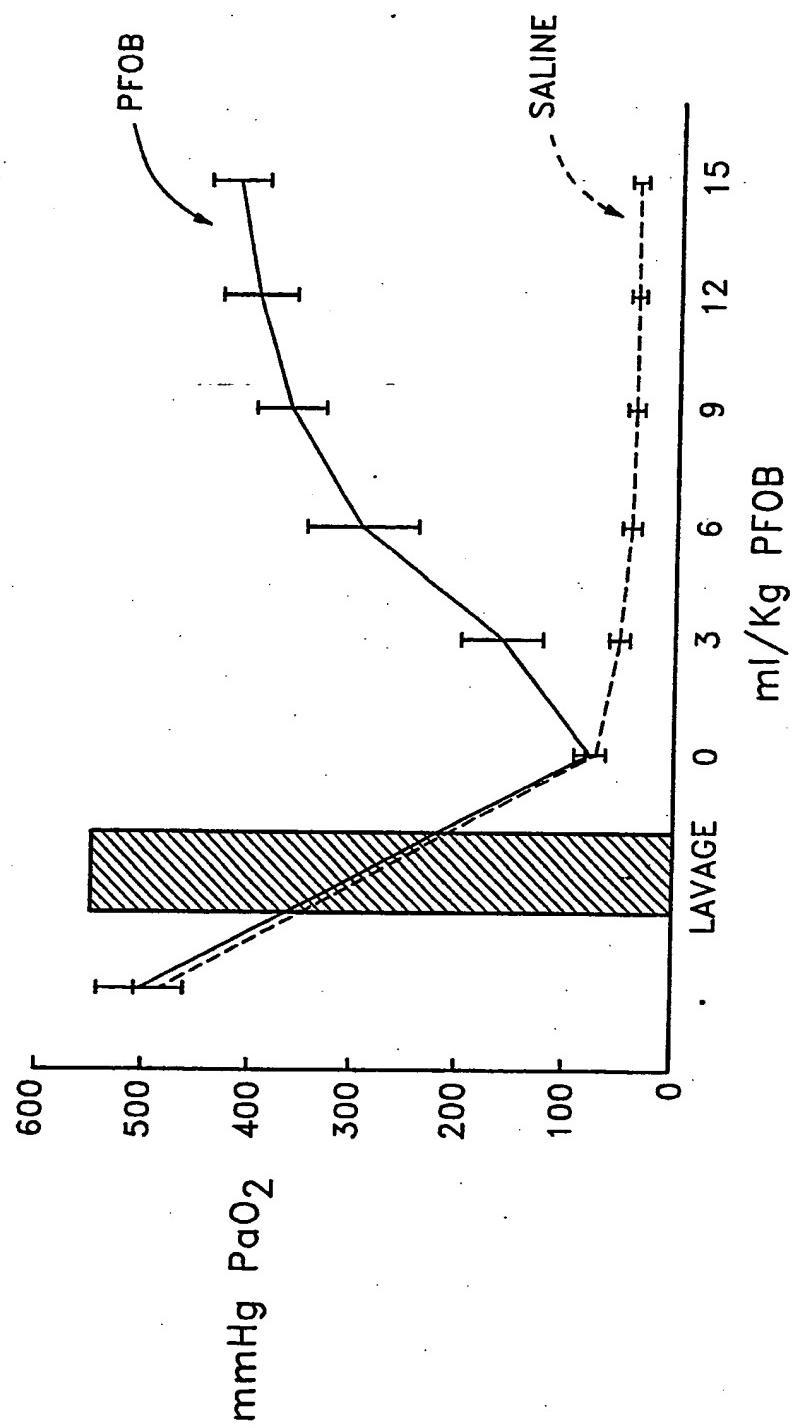


FIG. I

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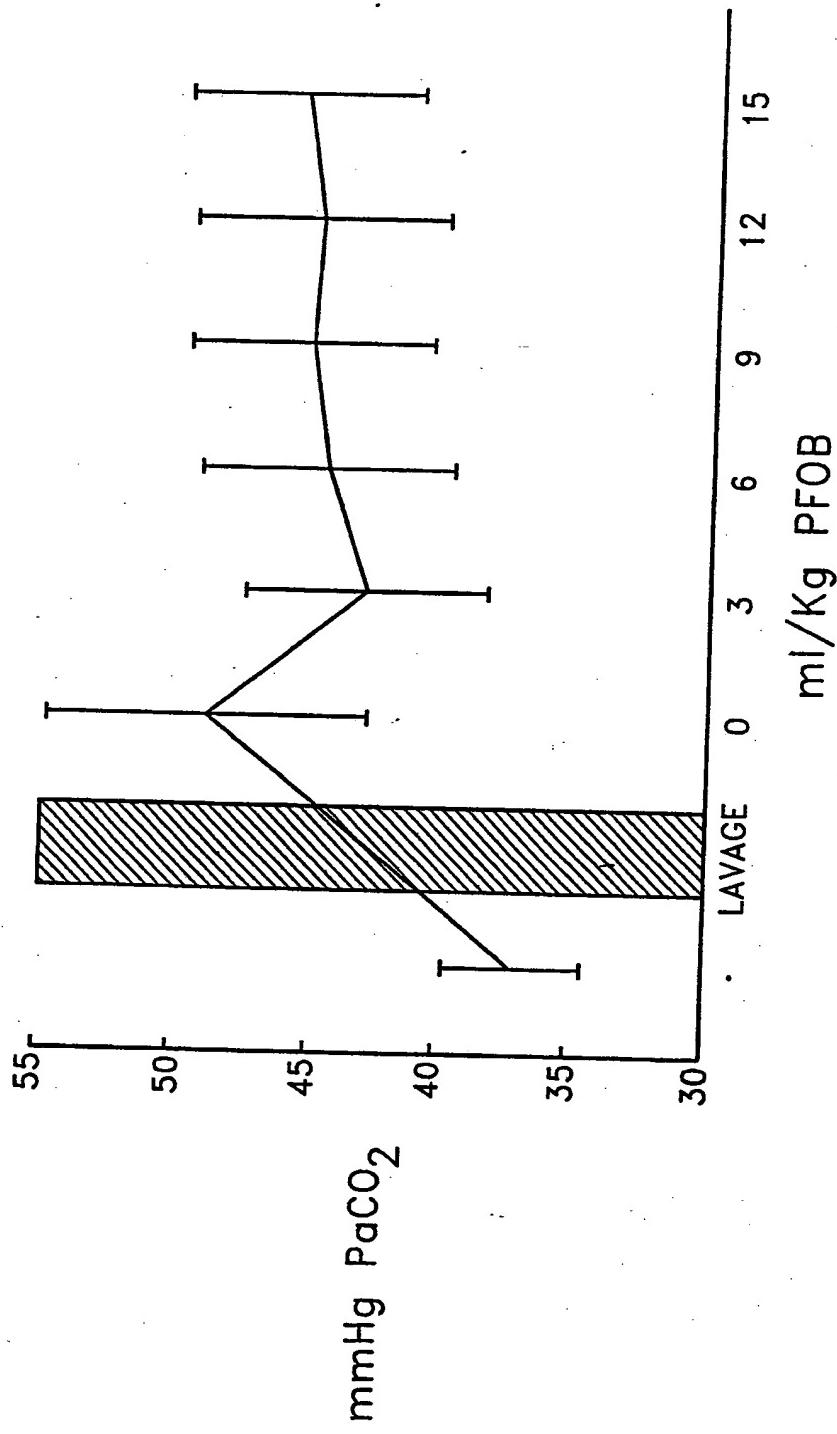


FIG. 2

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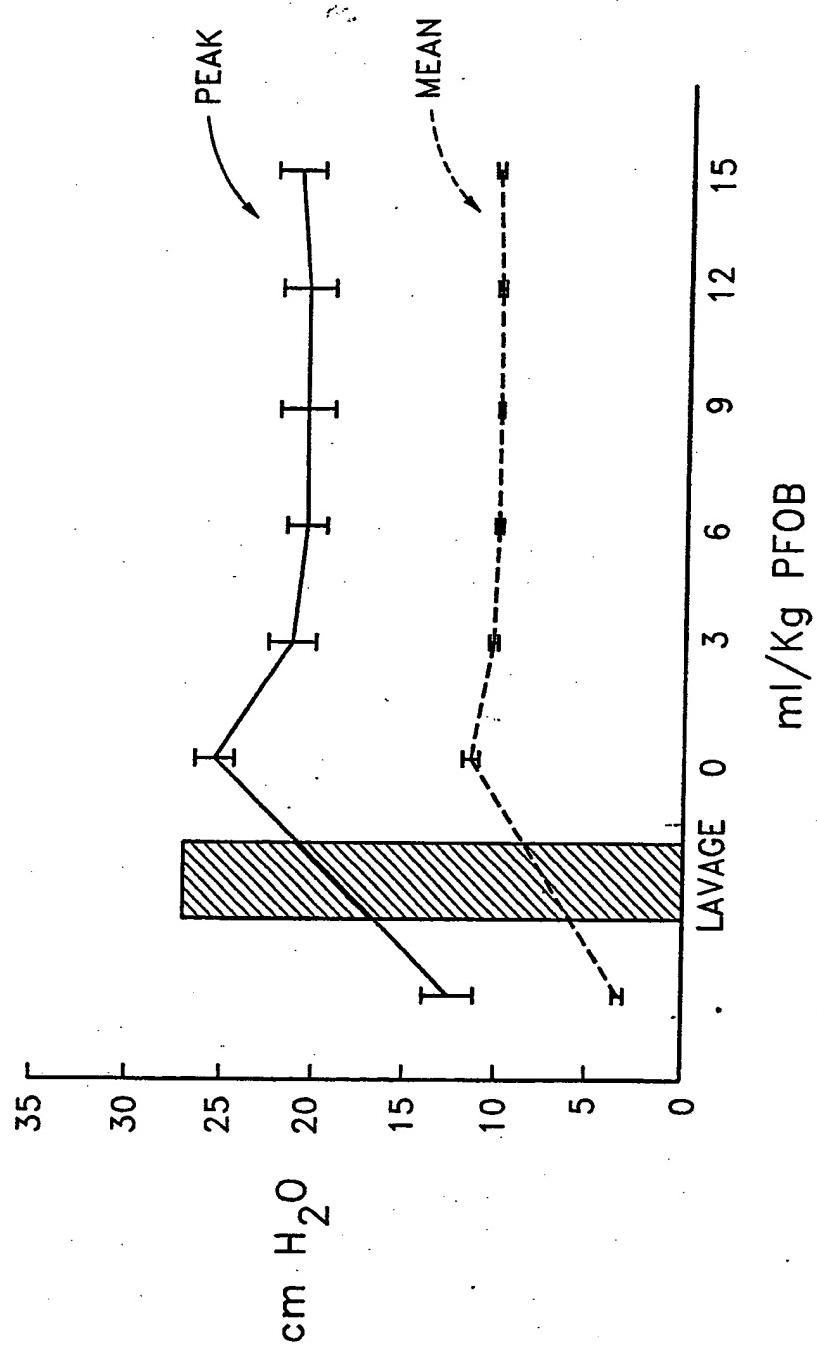


FIG. 3

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/03660

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC  
**Int.C1.5** A 61 K 31/02 A 61 K 31/08

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System	Classification Symbols
<b>Int.C1.5</b>	A 61 K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>

## III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
<b>A</b>	US,A,3975512 (LONG, Jr.) 17 August 1976, see column 1, lines 18-25; column 2, lines 29-34,63-65; claims (cited in the application) ---	1-27
<b>X</b>	Research in Experimental Medicine, vol. 188, no. 6, 1988, Springer-Verlag, B. WIDJAJA et al.: "Mechanical properties of isolated fetal miniature pig lungs after substitution with fluorocarbons", pages 425-432, see the entire document ---	1,8,10-16,18-20
<b>X</b>	DE,A,2245299 (ALLIED CHEMICALS CORP.) 26 April 1973, see pages 1,2,4; examples 1,2,3; claims ---	1,3,7,8,14-17,20 -/-

<sup>6</sup> Special categories of cited documents :<sup>10</sup>

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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<sup>T</sup> later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

<sup>X</sup> document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

<sup>Y</sup> document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

<sup>&</sup> document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

23-07-1992

Date of Mailing of this International Search Report

26.08.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

GOETZ G.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	Derwent-Information Service, file WPIL, accession no. 91-354366 [49], Derwent Publications Ltd, London, GB, & CA,A,2035492 (SEKINS) 20 September 1991, see the entire abstract ---	1-3,5,7 -9,11, 14-17, 21
X	WO,A,9103267 (SEKINS et al.) 21 March 1991, see the abstract, pages 5,6,9A,10; claims 3-17,46,63-74 -----	1-3,5,7 -9,11, 14-17, 21

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9203660  
SA 60293

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on 13/08/92.  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 3975512	17-08-76	US-A-	4073879	14-02-78
		CA-A-	973094	19-08-75
		DE-A,C	2163191	29-06-72
		FR-A,B	2118977	04-08-72
		GB-A-	1381879	29-01-75
DE-A- 2245299	26-04-73	FR-A-	2154709	11-05-73
WO-A- 9103267	21-03-91	AU-A-	4301389	08-04-91
		EP-A-	0491685	01-07-92

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